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(71) Applicant *(for all designated States except US)*: WORCESTER FOUNDATION FOR BIOMEDICAL RESEARCH [US/US]; 222 Maple Street, Shrewsbury, MA 01545-8000 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: ZAMECNIK, Paul, A. [US/US]; 29 LeBeaux Drive, Shrewsbury, MA 01545 (US).

(74) Agent: KINDREGAN, Helen; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).

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(57) Abstract

Methods of selectively inhibiting the growth of or killing prostatic cells, using antisense oligonucleotides to prostate specific genes, are disclosed. The oligonucleotides may have natural nucleic acid structures or may be modified oligonucleotides with enhanced stability or tissue specific targeting. The prostate specific genes to which the antisense may be directed include the AR and the αFGF gene. Pharmaceutical compositions including such antisense oligonucleotides are also described for use in the methods. The methods and products are of particular utility in the treatment of benign prostatic hyperplasia or prostate cancer.

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ANTISENSE OLIGONUCLEOTIDE CHEMOTHERAPY FOR BENIGN HYPERPLASIA OR CANCER OF THE PROSTATE

Field of the Invention

The present invention relates to the field of chemotherapy for hyperplasias and cancers and, in particular, to chemotherapy for benign hyperplasia or cancer of the prostate. In addition, the invention relates to the field of antisense oligonucleotides and their use in human hyperplasia and cancer therapy.

Background of the Invention

Treatment of carcinoma of the prostate was one of the first successes of cancer chemotherapy, using the therapeutic program of castration and/or anti-androgen hormonal treatments introduced by Charles Huggins in the 1940s. A remarkable relief of symptoms and objective regression of bony metastases occurs under this endocrine therapeutic program. Unfortunately, after a "golden period" which lasts roughly 18 months, regrowth of the prostate cancer cells occurs and, in the later stages of the disease, sensitivity to and repression by anti-androgen hormonal therapy ceases. The conventional regimen of combined chemotherapeutic agents also is typically ineffective after the golden period, and a downhill clinical course follows, terminating in death.

A key problem had been the silent onset of cancer of the prostate, with growth beyond its capsule and metastasis to bone too frequently occurring before the first visit to a physician. During the last half dozen years, there has been increasing recognition of the importance of early diagnosis and significant improvements in the available tests. As a consequence of early diagnosis, detection of prostatic cancer still contained within its capsule has become more frequent. For this situation, radical prostatectomy has largely supplanted the traditional castration/estrogen therapy. Radiation targeted to the prostate itself and to any proximal capsular infiltration has also become a prominent modality of therapy. When these two therapeutic approaches fail to halt progression of the disease, which is all too often (see, e.g., Gittes (1991); and Catalona (1994)), the prospect of benefit from available chemotherapy is gloomy.

Less severe but more common than prostatic cancer is benign prostatic hyperplasia (BPH). This condition may be a precursor to full blown prostatic cancer or may continue for decades without evolving into the deadly carcinoma. Depending upon the degree of hypertrophy

and the age of the patient, treatment may range from "watchful waiting" to more aggressive approaches employing anti-androgen hormonal therapy, transurethral resection, or radical prostatectomy (see, e.g., Catalona (1994)).

The androgen receptor (AR) binds the male hormone testosterone and, acting at the transcriptional level, regulates the growth of normal prostatic cells. A cDNA for the human AR was disclosed by Lubahn et al. (1988). As noted above, anti-androgen or estrogen hormonal therapy, including physical or chemical castration, may be effective against early stage prostate cancer but, after a period of roughly 18 months, the patient becomes refractory to the hormonal therapy. The relapse is believed to be the result of the development or clonal selection of androgen-independent tumor cells in which the AR has mutated or been lost (see, e.g., Taplin, et al. (1995); Klocker, et al. (1994). Interestingly, in murine androgen-independent prostatic cancer cells, transfection with an AR cDNA has been shown to inhibit growth in the presence of testosterone (Suzuki, et al. (1994)).

The acidic fibroblast growth factor (αFGF), also known as the heparin binding growth factor type one (HBGF-1), is an androgen-regulated mitogen produced by prostatic cells. An mRNA sequence for a human allele of αFGF was disclosed in Harris, et al. (1991). Mansson, et al. (1989) found that αFGF was expressed in normal immature rat prostate but not in normal mature rat prostate. In cancerous rat prostatic cell lines, they found αFGF expression similar to that in immature rat prostate.

Summary of the Invention

The present invention provides methods for treating a patient diagnosed as having benign prostatic hyperplasia or a prostatic cancer. The methods include administering to the patient a therapeutically effective amount of a composition comprising an antisense oligonucleotide which selectively hybridizes to an AR or αFGF gene or mRNA sequence of the patient, thereby inhibiting the expression of the AR or αFGF gene or mRNA sequence. This inhibition of the AR or αFGF genes or mRNAs by antisense oligonucleotides results in a significant inhibition of the growth or survival of prostatic cells. As a result, the methods provide a useful new means of treating benign prostatic hyperplasia and prostatic cancer. The methods are particularly useful in treating prostate cancer patients who have become refractory to anti-androgen hormonal therapy.

The AR antisense oligonucleotides may comprise at least 10 consecutive bases from SEQ

ID NO.: 1, at least 10 consecutive bases from a genomic sequence corresponding to SEQ ID NO.: 1, or oligonucleotides that hybridize to the complements of these sequences under physiological conditions. More preferably, the antisense oligonucleotides comprise at least 15 consecutive bases, and most preferably, 20-30 consecutive bases from the above-described sequences.

The αFGF antisense oligonucleotides may comprise at least 10 consecutive bases from any one of SEQ ID NO.: 2, SEQ ID NO.: 3 or SEQ ID NO.: 4, at least 10 consecutive bases from the joined exons of SEQ ID NO.: 2, SEQ ID NO.: 3 and SEQ ID NO.: 4; or oligonucleotides that hybridize to the complements of these sequences under physiological conditions. More preferably, the antisense oligonucleotides comprise at least 15 consecutive bases, and most preferably, 20-30 consecutive bases from the above-described sequences.

Examples of sequences of the invention include, but are not limited to, those disclosed as SEQ ID NO.: 5, SEQ ID NO.: 6, SEQ ID NO.: 7, and SEQ ID NO.: 8.

In preferred embodiments, all of the above-described oligonucleotides are modified oligonucleotides. In one set of embodiments, the modified oligonucleotide includes at least one synthetic internucleoside linkage such as a phosphorothioate, alkylphosphonate, phosphorodithioate, phosphate ester, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester.

In other embodiments with modified oligonucleotides, the modified oligonucleotide has at least one low molecular weight organic group covalently bound to a phosphate group of said oligonucleotide. In another set of embodiments, the modified oligonucleotide has at least one low molecular weight organic group covalently bound to a 2' position of a ribose of said oligonucleotide. Such low molecular weight organic groups include lower alkyl chains or aliphatic groups (e.g., methyl, ethyl, propyl, butyl), substituted alkyl and aliphatic groups (e.g., aminoethyl, aminopropyl, aminohydroxyethyl, aminohydroxypropyl), small saccharides or glycosyl groups.

In another set of embodiments the modified oligonucleotide has covalently attached thereto a prostate-targeting compound such as an androgen, androgen derivative, estrogen, estrogen derivative, estramustine, emcyt or estracyt.

In preferred embodiments, the antisense oligonucleotides are administered intravenously at a dosage between 1.0 μg and 100 mg per kg body weight of the patient.

The present invention also provides for any or all of the above-described antisense oligonucleotides, including the various modified oligonucleotides, in a pharmaceutical composition. The antisense oligonucleotides are admixed with a sterile pharmaceutically acceptable carrier in a therapeutically effective amount such that the isolated antisense oligonucleotide selectively hybridizes to the AR or αFGF gene or mRNA sequence when administered to a patient. A pharmaceutical kit is also provided in which such a pharmaceutical composition is combined with a pharmaceutically acceptable carrier for intravenous administration.

The methods and products of the present invention further include antisense oligonucleotides, as described above, directed at a PSA gene, a probasin gene, an estrogen receptor gene, a telomerase gene, a prohibitin gene, a src gene, a ras gene, a myc gene, a blc-2 gene, a protein kinase-A gene, a plasminogen activator urokinase gene and a methyl transferase gene.

Detailed Description of the Invention

The present invention provides new methods for the treatment of cancer of the prostate and pharmaceutical compositions useful therefor. It is now disclosed that antisense oligonucleotides complementary to genes which are expressed predominantly or strongly in prostatic cells are effective for inhibiting the growth of and/or killing hyperplastic or cancerous cells of prostatic origin. In particular, the present invention provides oligonucleotides, including modified oligonucleotides, which have antisense homology to a sufficient portion of either the AR or αFGF gene such that they inhibit the expression of that gene. Surprisingly, inhibition of either of these genes, even in androgen-resistant prostatic cancer cells, inhibits the growth of these cells. Because the antisense oligonucleotides of the invention can be administered systemically but selectively inhibit prostate cells, the present invention has particular utility in late stage prostate cancer which has metastasized.

Definitions

In order to describe more clearly and concisely the subject matter of the present invention, the following definitions are provided for specific terms used in the claims appended hereto:

AR. As used herein, the abbreviation "AR" refers to the androgen receptor well known

in the art and described in the various references cited herein. A cDNA sequence of the human AR gene was disclosed in Lubahn et al. (1988). The Lubahn et al. (1988)sequence is available on GenBank (Accession number J03180) and is reproduced here as SEQ. ID NO.: 1. The translation initiation codon of this gene is found at base positions 363-365 and the stop codon is at positions 3120-3122 of SEQ ID NO.: 1. As will be obvious to one of ordinary skill in the art, other alleles of the AR gene, including other human alleles and homologues from other mammalian species, encoding an AR protein and hybridizing to SEQ ID NO.: 1 under stringent hybridization conditions, will exist in natural populations and are embraced by the term "AR gene" as used herein.

αFGF. As used herein, the term "αFGF" refers to the αFGF protein known in the art and described in the various references cited herein. The genomic DNA of one allele of the human αFGF gene has been partially sequenced and was disclosed in Wang et al. (1989). The Wang et al.(1989) sequences cover the three exons of the αFGF gene as well as some 5', 3' and intron sequences. These sequences are available on GenBank (Accession numbers M23017, M23086 and M23087) and are reproduced here as SEQ. ID NO.: 2, SEQ ID NO.: 3 and SEQ ID NO.: 4. A partial cDNA sequence for a human αFGF gene also may be found in Harris et al. (1991). The locations of the exons are located in the sequence listings. The translation initiation codon is found at positions 602-604 of SEQ ID NO.: 2 and the stop codon is found at positions 496-498. In addition, as will be obvious to one of ordinary skill in the art, other alleles of the αFGF gene, including other human alleles and homologues from other mammalian species, encoding an αFGF protein and hybridizing to one or more of SEQ ID NO.: 2, SEQ ID NO.: 3 or SEQ ID NO.: 4 under stringent hybridization conditions, will exist in natural populations and are embraced by the term "αFGF gene" as used herein.

Antisense Oligonucleotides. As used herein, the term "antisense oligonucleotide" or "antisense" describes an oligonucleotide that is an oligoribonucleotide, oligodeoxyribonucleotide, modified oligoribonucleotide, or modified oligodeoxyribonucleotide which hybridizes under physiological conditions to DNA comprising a particular gene or to an mRNA transcript of that gene and, thereby, inhibits the transcription of that gene and/or the translation of that mRNA. In particular, by an "AR-antisense oligonucleotide" and by an "αFGF-antisense oligonucleotide" are meant oligonucleotides which hybridize under physiological conditions to the AR gene/mRNA or αFGF gene/mRNA and, thereby, inhibit

transcription/translation of the AR and αFGF genes/mRNAs, respectively. The antisense molecules are designed so as to interfere with transcription or translation of AR or αFGF upon hybridization with the target. Those skilled in the art will recognize that the exact length of the antisense oligonucleotide and its degree of complementarity will depend upon the specific target selected, including the sequence of the target and the particular bases which comprise that sequence. It is preferred that the antisense oligonucleotide be selected so as to hybridize selectively with the target under physiological conditions, i.e., to hybridize substantially more to the target sequence than to any other sequence in the target cell under physiological conditions.

Stringent hybridization conditions. As used herein, the term "stringent hybridization conditions" means hybridization conditions from 30°C-60°C and from 5x to 0.1x SSC. Highly stringent hybridization conditions are at 45°C and 0.1x SSC. "Stringent hybridization conditions" is a term of art understood by those of ordinary skill in the art. For any given nucleic acid sequence, stringent hybridization conditions are those conditions of temperature and buffer solution which will permit hybridization of that nucleic acid sequence to its complementary sequence and not to substantially different sequences. The exact conditions which constitute "stringent" conditions, depend upon the length of the nucleic acid sequence and the frequency of occurrence of subsets of that sequence within other non-identical sequences. By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, one of ordinary skill in the art can, without undue experimentation, determine conditions which will allow a given sequence to hybridize only with identical sequences. Suitable ranges of such stringency conditions are described in Krause, M.H.. and S.A. Aaronson, Methods in Enzymology, 200:546-556 (1991). As used herein with respect to in vivo hybridization conditions, the term "physiological conditions" is considered functionally equivalent to the in vitro stringent hybridization conditions.

I. Design of AR and αFGF Antisense Oligonucleotides

The present invention depends, in part, upon the discovery that the selective inhibition of the expression of AR or αFGF by antisense oligonucleotides in prostatic cells effectively inhibits cell growth and/or causes cell death.

Based upon SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3 and SEQ ID NO.: 4, or upon allelic or homologous genomic or cDNA sequences, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense molecules for use in accordance with the

present invention. In order to be sufficiently selective and potent for AR or αFGF inhibition, such antisense oligonucleotides should comprise at least 10 and, more preferably, at least 15 consecutive bases which are complementary to the AR or αFGF mRNA transcripts. Most preferably, the antisense oligonucleotides comprise a complementary sequence of 20-30 bases. Although oligonucleotides may be chosen which are antisense to any region of the AR or αFGF genes or mRNA transcripts, in preferred embodiments the antisense oligonucleotides correspond to N-terminal or 5' upstream sites such as translation initiation, transcription initiation or promoter sites. In addition, 3'-untranslated regions or telomerase sites may be targeted. Targeting to mRNA splicing sites has also been used in the art but may be less preferred if alternative mRNA splicing occurs. In addition, the AR or αFGF antisense is, preferably, targeted to sites in which mRNA secondary structure is not expected (see, e.g., Sainio et al. (1994)) and at which proteins are not expected to bind. Finally, although, SEQ ID NO.: 1 discloses a cDNA sequence and SEQ ID NO.: 2, SEQ ID NO.:3 and SEQ ID NO.: 4 disclose genomic DNA sequences, one of ordinary skill in the art may easily derive the genomic DNA corresponding to the cDNA of SEQ ID NO.: 1 and may easily obtain the cDNA sequence corresponding to SEQ ID NO.: 2, SEQ ID NO.:3 and SEQ ID NO.: 4. Thus, the present invention also provides for antisense oligonucleotides which are complementary to the genomic DNA corresponding to SEQ ID NO.: 1 and the cDNA corresponding to SEQ ID NO.: 2, SEQ ID NO.: 3 and SEQ ID NO.: 4. Similarly, antisense to allelic or homologous cDNAs and genomic DNAs are enabled without undue experimentation.

As will be understood by one of ordinary skill in the art, the antisense oligonucleotides of the present invention need not be perfectly complementary to the AR or αFGF genes or mRNA transcripts in order to be effective. Rather, some degree of mismatches will be acceptable if the antisense oligonucleotide is of sufficient length. In all cases, however, the oligonucleotides should have sufficient length and complementarity so as to hybridize to an AR or αFGF transcript under physiological conditions. Preferably, of course, mismatches are absent or minimal. In addition, although it is not recommended, the antisense oligonucleotides may have one or more non-complementary sequences of bases inserted into an otherwise complementary antisense oligonucleotide sequence. Such non-complementary sequences may "loop" out of a duplex formed by an AR or αFGF transcript and the bases flanking the non-complementary region. Therefore, the entire oligonucleotide may retain an inhibitory effect despite an

apparently low percentage of complementarity. Of particular importance in this respect is the use of self-stabilized or hairpin oligonucleotides. Such oligonucleotides, or modified oligonucleotides, have a sequence at the 5' and/or 3' end which is capable of folding over and forming a duplex with itself. The duplex region, which is preferably at least 4-6 bases joined by a loop of 3-6 bases, stabilizes the oligonucleotide against degradation. These self-stabilized oligonucleotides are easily designed by adding the inverted complement of a 5' or 3' AR or αFGF sequence to the end of the oligonucleotide (see, e.g., Table 1, SEQ ID NO.: 6 and SEQ ID NO.: 7; Tang, J.-Y., et al. (1993) Nucleic Acids Res. 21:2729-2735).

In one set of embodiments, the AR and αFGF antisense oligonucleotides of the invention may be composed of "natural" deoxyribonucleotides, ribonucleotides, or any combination thereof. That is, the 5' end of one nucleotide and the 3' end of another nucleotide may be covalently linked, as in natural systems, via a phosphodiester internucleoside linkage. These oligonucleotides may be prepared by art recognized methods which may be carried out manually or by an automated synthesizer.

In preferred embodiments, however, the antisense oligonucleotides of the invention also may include "modified" oligonucleotides. That is, the oligonucleotides may be modified in a number of ways which do not prevent them from hybridizing to their target but which enhance their stability or targeting to prostatic cells or which otherwise enhance their therapeutic effectiveness. The term "modified oligonucleotide" as used herein describes an oligonucleotide in which (1) at least two of its nucleotides are covalently linked via a synthetic internucleoside linkage (i.e., a linkage other than a phosphodiester linkage between the 5' end of one nucleotide and the 3' end of another nucleotide) and/or (2) a chemical group not normally associated with nucleic acids has been covalently attached to the oligonucleotide.

Preferred synthetic internucleoside linkages are phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamidate, and carboxymethyl esters. Further, one or more of the 5'→3' phosphate group may be covalently joined to a low molecular weight (e.g., 15-500 Da) organic group. Such low molecular weight organic groups include lower alkyl chains or aliphatic groups (e.g., methyl, ethyl, propyl, butyl), substituted alkyl and aliphatic groups (e.g., aminoethyl, aminopropyl, aminohydroxyethyl, aminohydroxypropyl), small saccharides or glycosyl groups. Other low molecular weight organic modifications include additions to the

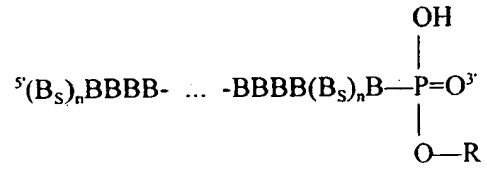
internucleoside phosphate linkages such as cholesteryl or diamine compounds with varying numbers of carbon residues between the amino groups and terminal ribose. Oligonucleotides with these linkages or other modifications can be prepared according to known methods (see, e.g., Agrawal and Goodchild (1987); Agrawal et al. (1988); Uhlmann et al. (1990); Agrawal et al. (1992); Agrawal (1993); and U.S. Pat. No. 5,149,798).

The term "modified oligonucleotide" also encompasses oligonucleotides with a covalently modified base and/or sugar. For example, modified oligonucleotides include oligonucleotides having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified oligonucleotides may include a 2'-O-alkylated ribose group such as a 2'-O-methylated ribose. In addition, modified oligonucleotides may include sugars such as arabinose instead of ribose. Alternatively, the modified oligonucleotides may be branched oligonucleotides. Unoxidized or partially oxidized oligonucleotides having a substitution in one or more nonbridging oxygen per nucleotide in the molecule are also considered to be modified oligonucleotides.

Also considered as modified oligonucleotides are oligonucleotides having prostate-targeting, nuclease resistance-conferring, or other bulky substituents and/or various other structural modifications not found *in vivo* without human intervention. The androgen receptor and other hormonal receptor sites on prostate cells allow for targeting antisense oligonucleotides specifically or particularly to prostatic cells. Attachment of the antisense oligonucleotides by a molecular "tether" (e.g., an alkyl chain) to estramustine, emcyt or estracyt (Sheridan and Tew (1991)), for example, may provide prostatic targeting and the possibility of covalent alkylation of host prostatic DNA. Estramustine targets particularly to the ventral prostate (Forsgren, et al. (1979)). Similarly, one may covalently attach androgen, estrogen, androgen or estrogen derivatives, or other prostate cell ligands to antisense oligonucleotides using tethers and conjugating linkages for prostatic targeting. Finally, one may of course covalently attach other chemotherapeutic agents (e.g., dexamethasone, vinblastine, etoposide) to the antisense oligonucleotides for enhanced effect.

The most preferred modified oligonucleotides are hybrid or chimeric oligonucleotides in which some but not all of the phosphodiester linkages, bases or sugars have been modified. Hybrid modified antisense oligonucleotides may be composed, for example, of stretches of ten

2'-O-alkyl nucleotides or ten phosphorothioate synthetic linkages at the 5' and/or 3' ends, and a segment of seven unmodified oligodeoxynucleotides in the center, or of similar terminal segments of alkyl phosphonates, with central P=S or P=O oligonucleotides (Agrawal, et al. (1990); Metelev, et al. (1994)). The currently most preferred modified oligonucleotides are 2'-O-methylated hybrid oligonucleotides. Since degradation occurs mainly at the 3' end, secondarily at the 5' end, and less in the middle, unmodified oligonucleotides located at this position can activate RNase H, and yet are degraded slowly. Furthermore, the T_m of such a 27-mer is approximately 20°C higher than that of a 27-mer all phosphorothioate oligodeoxynucleotide. This greater affinity for the targeted genomic area can result in greater inhibiting efficacy. Obviously, the number of synthetic linkages at the termini need not be ten and synthetic linkages may be combined with other modifications, such as alkylation of a 5' or 3' phosphate, or 2'-O-alkylation. Thus, merely as another example, one may produce a modified oligonucleotide with the following structure, where B represents any base, R is an alkyl, aliphatic or other substituent, the subscript S represents a synthetic (e.g. phosphorothioate) linkage, and each n is an independently chosen integer from 1 to about 20:



II. Products and Methods of Treatment for BPH and Prostate Cancer

The methods of the present invention represent new and useful additions to the field of benign prostate hyperplasia or prostate cancer therapy. In particular, the methods of the present invention are especially useful for late stage prostate cancer in which metastases have occurred and in which the cells have become resistant to estrogen or anti-androgen therapy. The methods may, however, also be used in benign prostate hyperplasia or early stage prostate cancer and may provide a substitute for more radical procedures such as transurethral resection, radical prostatectomy, or physical or chemical castration. The products of the present invention include the isolated antisense oligonucleotides described above. As used herein, the term "isolated" as applied to an antisense oligonucleotide means not covalently bound to and physically separated from the 5' and 3' sequences which flank the corresponding antisense sequence in nature.

Administration of the AR or αFGF antisense oligonucleotides may be oral, intravenous,

parenteral, cutaneous or subcutaneous. For BPH or when the site of a prostatic tumor is known, the administration also may be localized to the prostate or to the region of the tumor by injection to or perfusion of the site.

AR or αFGF antisense oligonucleotides may be administered as part of a pharmaceutical composition. Such a pharmaceutical composition may include the antisense oligonucleotides in combination with any standard physiologically and/or pharmaceutically acceptable carriers which are known in the art. The compositions should be sterile and contain a therapeutically effective amount of the antisense oligonucleotides in a unit of weight or volume suitable for administration to a patient. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. The term "physiologically acceptable" refers to a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism. The characteristics of the carrier will depend on the route of administration. Physiologically and pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials which are well known in the art. The pharmaceutical composition of the invention may also contain other active factors and/or agents which inhibit prostate cell growth or increase cell death. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect or to minimize side-effects caused.

The pharmaceutical composition of the invention may be in the form of a liposome in which the AR or αFGF antisense oligonucleotides are combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers which are in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Pat. No. 4,235,871; U.S. Pat. No. 4,501,728; U.S. Pat. No. 4,837,028; and U.S. Pat. No. 4,737,323.

The pharmaceutical composition of the invention may further include compounds such as cyclodextrins and the like which enhance delivery of oligonucleotides into cells. When the composition is not administered systemically but, rather, is injected at the site of the target cells, cationic detergents (e.g. Lipofectin) may be added to enhance uptake.

When a therapeutically effective amount of AR or αFGF antisense oligonucleotides is administered orally, the oligonucleotides will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder may contain from about 5 to 95% of the AR and/or αFGF antisense oligonucleotides and preferably from about 25 to 90% of the oligonucleotides. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition may contain from about 0.5 to 90% by weight of an AR and/or αFGF antisense oligonucleotide and preferably from about 1 to 50% of the oligonucleotide.

When a therapeutically effective amount of an AR or αFGF antisense oligonucleotide is administered by intravenous, cutaneous or subcutaneous injection, the oligonucleotides will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to the antisense oligonucleotides, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or another vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

In preferred embodiments, when the target cells are readily accessible, administration of the antisense oligonucleotides is localized to the region of the targeted cells in order to maximize the delivery of the antisense and to minimize the amount of antisense needed per treatment. Thus, in one preferred embodiment, administration is by direct injection at or perfusion of the site of the targeted cells, such as a tumor. Alternatively, the antisense oligonucleotides may be adhered to small particles (e.g., microscopic gold beads) which are impelled through the membranes of the target cells (see, e.g., U.S. Pat. No. 5,149,655).

In another series of embodiments, a recombinant gene is constructed which encodes an

AR or αFGF antisense oligonucleotide and this gene is introduced within the targeted cells on a vector. Such an AR or αFGF antisense gene may, for example, consist of the normal AR or αFGF sequence, or a subset of the normal sequences, operably joined in reverse orientation to a promoter region. An operable antisense gene may be introduced on an integration vector or may be introduced on an expression vector. In order to be most effective, it is preferred that the antisense sequences be operably joined to a strong eukaryotic promoter which is inducible or constitutively expressed.

In all of the above-described methods of treatment, the AR and/or αFGF antisense oligonucleotides are administered in therapeutically effective amounts. As used herein, the term "therapeutically effective amount" means that amount of antisense which, under the conditions of administration, including mode of administration and presence of other active components, is sufficient to result in a meaningful patient benefit, i.e., the killing or inhibition of the growth of target cells.

The amount of AR and/or αFGF antisense oligonucleotides in the pharmaceutical composition of the present invention will depend not only upon the potency of the antisense but also upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of antisense with which to treat each individual patient. Initially, the attending physician will administer low doses of the inhibitor and observe the patient's response. Larger doses of antisense may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. In preferred embodiments, it is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 1.0 μg to about 100 mg of oligonucleotide per kg body weight.

The duration of intravenous therapy using the pharmaceutical compositions of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. Because a bolus of oligonucleotides, particularly highly negatively-charged phosphorothioate modified oligonucleotides, may have adverse side effects (e.g., rapid lowering of blood pressure), slow intravenous administration is preferred. Thus, intravenous administration of therapeutically effective amounts over a 12-24 hour period are contemplated. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

The following examples of the use of AR and αFGF antisense are presented merely to illustrate some of the oligonucleotides, including modified oligonucleotides, that may be employed according to the present invention. The particular oligonucleotides used, therefore, should not be construed as limiting of the invention but, rather, as indicative of the wide range of oligonucleotides which may be employed. As will be obvious to one of ordinary skill in the art in light of the present disclosure, a great many equivalents to the presently disclosed antisense oligonucleotides and disclosed methods are now available. In particular, other antisense oligonucleotides substantially complementary to subsets of SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3 or SEQ ID NO.: 4 and chemical modifications of the same which do not prevent hybridization under physiological conditions, are contemplated as equivalents of the examples presented below. In general, the use of prostate specific antisense oligonucleotides is contemplated as a method of selectively inhibiting the growth of or killing prostatic cells. In particular, the use of antisense oligonucleotides to the estrogen receptor, PSA, probasin, telomerase, prohibitin, src, ras, myc, blc-2, protein kinase-A, plasminogenctivator urokinase and methyl transferase genes is contemplated for the treatment of benign prostatic hyperplasia or prostatic cancer.

Experimental Examples

The PC3-1435 permanent cell line of human prostatic cancer, obtained from the American Type Culture Collection, was grown in monolayer culture: The PC3-1435 cells are from an osseous metastasis and are androgen-insensitive. Cells were grown in Dulbecco's medium supplemented with 10 percent fetal calf serum, glutamate, pyruvate, penicillin and streptomycin, in 25-150 cm flasks, incubated at 37°C in 6 percent CO_2-air.

A number of AR and αFGF antisense oligonucleotides were tested for their inhibitory effect on prostatic cells. The base sequences of these oligonucleotides are disclosed as SEQ ID NO.: 5 through SEQ ID NO.: 8. SEQ ID NO.: 5 is antisense to positions 927-953 of the AR gene (SEQ ID NO.: 1). SEQ ID NO.: 6 is a self-stabilized or hairpin oligonucleotide. The first 21 bases are complementary to positions 916-936 of the AR gene. The remaining eight are identical to positions 920-927 of the gene, allowing formation of a 3' hairpin. SEQ ID NO.: 7 is another self-stabilized antisense oligonucleotide. The first 21 bases of this oligonucleotide are complementary to positions 927-947 of the AR gene. The remaining eight are identical to

positions 931-938 of the gene, allowing for formation of a 3' hairpin. Finally, SEQ ID NO.: 8 is an antisense sequence corresponding to positions 611-635 of the αFGF gene.

Table 1 shows some of the antisense oligonucleotides tested. The numbers at the left of each sequence correspond to the sequence numbers in the sequence listing. Antisense oligonucleotides with unmodified or natural internucleoside linkages (P=O) and oligonucleotides with all phosphorothioate synthetic linkages (P=S) were tested. In addition, modified oligonucleotides were tested in which just the terminal two phosphodiester linkages at each end had been replaced by phosphorothioate synthetic linkages (shown as a subscript S between nucleotides in Table 1) and/or in which small organic chemical groups (e.g., 2-hydroxy-3-amino-propyl, propylamine) were added to the 3' terminal phosphate or the penultimate 3' phosphate.

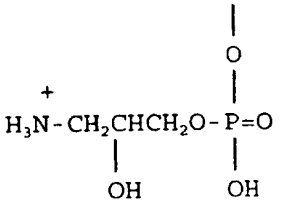
Growth of the PC3-1435 cell line in tissue culture monolayers was consistently inhibited by addition of phosphorothioate-modified oligodeoxynucleotides targeted against the AR or αFGF genes and incubation for 24-48 hours thereafter. As the concentration of modified oligonucleotides is decreased from the 10-20 μM level, most effective inhibition occurs with specific antisense oligodeoxynucleotides at the 2-5 μM level, as contrasted with mismatched oligodeoxynucleotides (see Tables 2 and 3).

While the effects on cell growth (i.e. cell numbers) are readily manifest, visual substage microscopy of wells revealed additional features of the inhibition events using AR antisense oligonucleotides against PC3-1435 cells. The first evidence of antisense inhibition is rupture of the monolayer fabric. The stellate cells in a confluent culture lose contact with their neighbors, round up individually or in clumps, become pyknotic, and cease growing, as examined on successive days. There is an early loss of adhesiveness to the floor of the plastic wells. These changes are more severe (see Table 4) than those measured by ^{3}H-thymidine incorporation into DNA, in other words more drastic than the impairment of DNA synthesis.

Each of the above-mentioned references and patents are incorporated by reference.

TABLE 1

Antisense Oligonucleotides

	Sequence	Target
#5	$^{5'}$CTG-CTG-CTG-TTG-CTG-AAG-GAG-TTG-CAT$^{3'}$	Androgen receptor, P=S
#5	$^{5'}$CTG-CTG-CTG-TTG-CTG-AAG-GAG-TTG-CAT$^{3'}$	Androgen receptor, P=O
#5	$^{5'}C_sT_sG$-CTG-CTG-TTG-CTG-AAG-GAG-TTG-$C_sA_sT^{3'}$	Androgen receptor, P=S termini
#5	$^{5'}$CTG-CTG-CTG-TTG-CTG-AAG-GAG-TTG-CAT$^{3'}$ receptor, 	Androgen modified with organic group
#5	$^{5'}$CTG-CTG-CTG-TTG-CTG-AAG-GAG-TTG-CA-O-P(=O)(-O-T$^{3'}$)-$CH_3CH_2CH_2NH$ receptor,	Androgen modified with organic group
#6	$^{5'}$GGA-GTT-GCA-TGG-TGC-TGG-CCT-CAG-CAC-CA$^{3'}$ receptor	Androgen 3' hairpin, P=S
#7	$^{5'}$CTG-TTG-CTG-AAG-GAG-TTG-CAT-AAC-TCC-TT$^{3'}$ receptor	Androgen 3' hairpin, P=S
#8	$^{5'}$GGG-CTG-TGA-AGG-TGG-TGA-TTT-CCC-C$^{3'}$	αFGF, P=S

#8 5'GGG-CTG-TGA-AGG-TGG-TGA-TTT-CCC-C3' αFGF, P=O

TABLE 2

^{3}H-thymidine incorporation into DNA PC3-1435

human prostate cancer tissue culture

Genes Targeted	Concentration (μM)	CPM†	% inhibition
Control (no oligo)	--	38,000	0
Androgen receptor, (P = S)	20	15,000	60
	5	20,000	48
Androgen receptor, (P = S)*	20	10,200	68
	5	24,000	25
Mismatch (P = S)	20	20,000	47
	5	27,000	30

† Averages of 3 separate wells

* 3' phosphate modified with -$CH_2CHOHCHNH_3$

TABLE 3

Degree of inhibition of DNA synthesis

in PC3-1435 prostate cancer tissue cultures

Genes targeted	Concentration (μM)	CPM †	% inhibition
Control (no oligo)	--	14,700	0
αFGF (P=S)	20	2,485	83
	5	4,500	69
Mismatch	20	6,990	51
	5	10,750	27

† Averages of 3 separate wells.

TABLE 4

Morphological Comparison of Treated and Control Cells

	Concentration μM			
Gene Target	20	10	5	2
αFGF (P=S)	4+	4+	1-1/2+	1+
Androgen receptor (P=S)	3+	3+	1+	1+
Mismatch (P=S)	1-1/2+	1/2+	0	0

Observation 24 hours after oligonucleotide addition. Damage: 4+ devastating; 3+ severe; 2+ serious; 1+ visible; 1/2+ slight; 0 none

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: WORCESTER FOUNDATION FOR BIOMEDICAL RESEARCH, INC.

(ii) TITLE OF INVENTION: ANTISENSE OLIGONUCLEOTIDE CHEMOTHERAPY FOR BENIGN HYPERPLASIA OR CANCER OF THE PROSTATE

(iii) NUMBER OF SEQUENCES: 8

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: WOLF, GREENFIELD & SACKS, P.C.
(B) STREET: 600 ATLANTIC AVENUE
(C) CITY: BOSTON
(D) STATE: MA
(E) COUNTRY: USA
(F) ZIP: 02210

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: TWOMEY, MICHAEL J.

(B) REGISTRATION NUMBER: 38,349

(C) REFERENCE/DOCKET NUMBER: W0461/7035

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 617-720-3500

(B) TELEFAX: 617-720-2441

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3569 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 363..3122

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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ACAGACTGTG AGCCTAGCAG GGCAGATCTT GTCCACCGTG TGTCTTCTTC TGCACGAGAC 180

TTTGAGGCTG TCAGAGCGCT TTTTGCGTGG TTGCTCCCGC AAGTTTCCTT CTCTGGAGCT 240

TCCCGCAGGT GGGCAGCTAG CTGCAGCGAC TACCGCATCA TCACAGCCTG TTGAACTCTT 300

CTGAGCAAGA GAAGGGGAGG CGGGGTAAGG GAAGTAGGTG GAAGATTCAG CCAAGCTCAA 360

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Met Glu Val Gln Leu Gly Leu Gly Arg Val Tyr Pro Arg Pro Pro
1 5 10 15

TCC AAG ACC TAC CGA GGA GCT TTC CAG AAT CTG TTC CAG AGC GTG CGC 455
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20 25 30

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Glu Val Ile Gln Asn Pro Gly Pro Arg His Pro Glu Ala Ala Ser Ala
35 40 45

GCA CCT CCC GGC GCC AGT TTG CTG CTG CTG CAG CAG CAG CAG CAG CAG 551
Ala Pro Pro Gly Ala Ser Leu Leu Leu Leu Gln Gln Gln Gln Gln Gln
50 55 60

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CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAA GAG     599
Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Glu
     65                  70                  75

ACT AGC CCC AGG CAG CAG CAG CAG CAG CAG GGT GAG GAT GGT TCT CCC     647
Thr Ser Pro Arg Gln Gln Gln Gln Gln Gln Gly Glu Asp Gly Ser Pro
 80                  85                  90                  95

CAA GCC CAT CGT AGA GGC CCC ACA GGC TAC CTG GTC CTG GAT GAG GAA     695
Gln Ala His Arg Arg Gly Pro Thr Gly Tyr Leu Val Leu Asp Glu Glu
                100                 105                 110

CAG CAA CCT TCA CAG CCG CAG TCG GCC CTG GAG TGC CAC CCC GAG AGA     743
Gln Gln Pro Ser Gln Pro Gln Ser Ala Leu Glu Cys His Pro Glu Arg
            115                 120                 125

GGT TGC GTC CCA GAG CCT GGA GCC GCC GTG GCC GCC AGC AAG GGG CTG     791
Gly Cys Val Pro Glu Pro Gly Ala Ala Val Ala Ala Ser Lys Gly Leu
        130                 135                 140

CCG CAG CAG CTG CCA GCA CCT CCG GAC GAG GAT GAC TCA GCT GCC CCA     839
Pro Gln Gln Leu Pro Ala Pro Pro Asp Glu Asp Asp Ser Ala Ala Pro
    145                 150                 155

TCC ACG TTG TCC CTG CTG GGC CCC ACT TTC CCC GGC TTA AGC AGC TGC     887
Ser Thr Leu Ser Leu Leu Gly Pro Thr Phe Pro Gly Leu Ser Ser Cys
160                 165                 170                 175

TCC GCT GAC CTT AAA GAC ATC CTG AGC GAG GCC AGC ACC ATG CAA CTC     935
Ser Ala Asp Leu Lys Asp Ile Leu Ser Glu Ala Ser Thr Met Gln Leu
                180                 185                 190

CTT CAG CAA CAG CAG CAG GAA GCA GTA TCC GAA GGC AGC AGC AGC GGG     983
Leu Gln Gln Gln Gln Gln Glu Ala Val Ser Glu Gly Ser Ser Ser Gly
            195                 200                 205
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AGA GCG AGG GAG GCC TCG GGG GCT CCC ACT TCC TCC AAG GAC AAT TAC 1031
Arg Ala Arg Glu Ala Ser Gly Ala Pro Thr Ser Ser Lys Asp Asn Tyr
210 215 220

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225 230 235

GCA GTG TCG GTG TCC ATG GGC CTG GGT GTG GAG GCG TTG GAG CAT CTG 1127
Ala Val Ser Val Ser Met Gly Leu Gly Val Glu Ala Leu Glu His Leu
240 245 250 255

AGT CCA GGG GAA CAG CTT CGG GGG GAT TGC ATG TAC GCC CCA CTT TTG 1175
Ser Pro Gly Glu Gln Leu Arg Gly Asp Cys Met Tyr Ala Pro Leu Leu
260 265 270

GGA GTT CCA CCC GCT GTG CGT CCC ACT CCT TGT GCC CCA TTG GCC GAA 1223
Gly Val Pro Pro Ala Val Arg Pro Thr Pro Cys Ala Pro Leu Ala Glu
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TGC AAA GGT TCT CTG CTA GAC GAC AGC GCA GGC AAG AGC ACT GAA GAT 1271
Cys Lys Gly Ser Leu Leu Asp Asp Ser Ala Gly Lys Ser Thr Glu Asp
290 295 300

ACT GCT GAG TAT TCC CCT TTC AAG GGA GGT TAC ACC AAA GGG CTA GAA 1319
Thr Ala Glu Tyr Ser Pro Phe Lys Gly Gly Tyr Thr Lys Gly Leu Glu
305 310 315

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Gly Glu Ser Leu Gly Cys Ser Gly Ser Ala Ala Ala Gly Ser Ser Gly
320 325 330 335

ACA CTT GAA CTG CCG TCT ACC CTG TCT CTC TAC AAG TCC GGA GCA CTG 1415
Thr Leu Glu Leu Pro Ser Thr Leu Ser Leu Tyr Lys Ser Gly Ala Leu
340 345 350

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GAC GAG GCA GCT GCG TAC CAG AGT CGC GAC TAC TAC AAC TTT CCA CTG   1463
Asp Glu Ala Ala Ala Tyr Gln Ser Arg Asp Tyr Tyr Asn Phe Pro Leu
            355                 360                 365

GCT CTG GCC GGA CCG CCG CCC CCT CCG CCG CCT CCC CAT CCC CAC GCT   1511
Ala Leu Ala Gly Pro Pro Pro Pro Pro Pro Pro Pro His Pro His Ala
        370                 375                 380

CGC ATC AAG CTG GAG AAC CCG CTG GAC TAC GGC AGC GCC TGG GCG GCT   1559
Arg Ile Lys Leu Glu Asn Pro Leu Asp Tyr Gly Ser Ala Trp Ala Ala
    385                 390                 395

GCG GCG GCG CAG TGC CGC TAT GGG GAC CTG GCG AGC CTG CAT GGC GCG   1607
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Gly Ala Ala Gly Pro Gly Ser Gly Ser Pro Ser Ala Ala Ala Ser Ser
                420                 425                 430

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            435                 440                 445

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Gly Gly Gly Gly Gly Gly Gly Gly Gly Glu Ala Gly Ala Val Ala Pro
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TAC GGC TAC ACT CGG CCC CCT CAG GGG CTG GCG GGC CAG GAA AGC GAC   1847
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Pro Tyr Pro Ser Pro Thr Cys Val Lys Ser Glu Met Gly Pro Trp Met
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Asp Ser Tyr Ser Gly Pro Tyr Gly Asp Met Arg Leu Glu Thr Ala Arg
        530                 535                 540

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Asp His Val Leu Pro Ile Asp Tyr Tyr Phe Pro Pro Gln Lys Thr Cys
    545                 550                 555

CTG ATC TGT GGA GAT GAA GCT TCT GGG TGT CAC TAT GGA GCT CTC ACA   2087
Leu Ile Cys Gly Asp Glu Ala Ser Gly Cys His Tyr Gly Ala Leu Thr
560                 565                 570                 575

TGT GGA AGC TGC AAG GTC TTC TTC AAA AGA GCC GCT GAA GGG AAA CAG   2135
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AAG TAC CTG TGC GCC AGC AGA AAT GAT TGC ACT ATT GAT AAA TTC CGA   2183
Lys Tyr Leu Cys Ala Ser Arg Asn Asp Cys Thr Ile Asp Lys Phe Arg
            595                 600                 605

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Met Thr Leu Gly Ala Arg Lys Leu Lys Lys Leu Gly Asn Leu Lys Leu
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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1082 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 602..770

(D) OTHER INFORMATION: /note= "SEGMENT 1 OF 3."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

AAGCTTCCCT TAACATACTA ACCCTTTACT TTCCCTGTTG TGTCCCTGAA AGGCCTCCTG 60

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CACCAACGCA ACGTGAGGGT GGAGGGCAGA ACCTTGGTCC TGGCCTCTCA GCTTTTGTGG 180

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GCCCGCGGAC TGCGGGCATC ACCTGGGCAG GCTGTGCTTA CTCACTACCC GGGAACCCTG 480

TGCCCTGGAG CTGTCCTTCC TCTCTTCAAA GTGCATTTTG TGCCTTTGCT GGAAGAACCG 540

ACTACAGGTT TGTTCAATTT CTTACAGTCT TGAAAGCGCC ACAAGCAGCA GCTGCTGAGC 600

CATGGCTGAA GGGGAAATCA CCACCTTCAC AGCCCTGACC GAGAAGTTTA ATCTGCCTCC 660

AGGGAATTAC AAGAAGCCCA AACTCCTCTA CTGTAGCAAC GGGGGCCACT TCCTGAGGAT 720

CCTTCCGGAT GGCACAGTGG ATGGGACAAG GGACAGGAGC GACCAGCACA GTAAGCCCAT 780

CTCTATGGCA CCCCCCTTCC CTTTCTGACA TCTTCTGTAG TCAAGGTGGG AGGAAGGTGC 840

ACATTTAAGT ACAGGTACTT GCTTCTCCAA GGTTCTATTC AGGCATGACA CATTCAGAGG 900

TGGAGTCACA TAAATGCGTA AAATGTCTGG GAAATGAAAA TAGGGACTTG TGGGGGCCAC 960

CACTTACCCA AACGTGTCCT ATTTCAAGTT TTTTAAAGCA CTCTCTGCTG ACCCAACAGA 1020

ACGGGCTGCC GGTGCTCAAT TGCTGTATGT TTTCCCAGGT TTCTGTAACT AGTGAAAGAT 1080

CT 1082

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 427 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 186..289
(D) OTHER INFORMATION: /note= "SEGMENT 2 OF 3. UNKNOWN NUMBER OF BP AFTER SEGMENT 1."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CAGCTTTCTT TGGAAGGCAA AGAAAAAGGG ACTGTATTTC TATGTTTTGA TTAATCTGAG 60

GCTCATCCTG AGGGCTCCGT GAAATGAATG AGCAGAATTT TCCATGGCCA ACTGTCCTGG 120

CTGCCGGGTC CTATCGGCAA AAGCGTAGTG TTTATTTACT TTTGCTCGTG TTATTTTTAT 180

TCCAGTTCAG CTGCAGCTCA GTGCGGAAAG CGTGGGGGAG GTGTATATAA AGAGTACCGA 240

GACTGGCCAG TACTTGGCCA TGGACACCGA CGGGCTTTTA TACGGCTCAG TAAGTATGAA 300

GCTGACATGC TTCCAGACGT TGGCCAAGGT TTGAGGTTTC CAGAAATCTT GTTACATGGA 360

GTGAGGCAAA CTATAAAGCA ACAATTAGTC TCTGTTTGTT ATTTTTTCCA GAAGGATTCC 420

CACCCTC 427

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 664 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 304..498
(D) OTHER INFORMATION: /note= "SEGMENT 3 OF 3. UNKNOWN NUMBER OF BP AFTER SEGMENT 2."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

TGAGGACTCT TAGAAGTGCT CTTATCAGTA GCATCTTAAT TACTTTACAA TGGATTTTAA 60

ATGGAAAGGA AGTTTACAAT AATAGCAAAT GCATATTGAC AGCTCTTTAG TGCCCGGTGC 120

TGTTCTAAGT CCTTATGACT ACCCTGTGAA ATAAGTTCCA CCATGACCCC AATTTTCCTG 180

AAAAGGAGAC TGAGGCATGG AGAGCTTTAG TATTTTGCCC AATGTCACAC AGCTAGTAAA 240

TGGGGACCCC CATGTGAAAC TACTCACTGA TTGTCCTACT CTCTTGTGGT TTTATCTTTT 300

TAGCAGACAC CAAATGAGGA ATGTTTGTTC CTGGAAAGGC TGGAGGAGAA CCATTACAAC 360

ACCTATATAT CCAAGAAGCA TGCAGAGAAG AATTGGTTTG TTGGCCTCAA GAAGAATGGG 420

AGCTGCAAAC GCGGTCCTCG GACTCACTAT GGCCAGAAAG CAATCTTGTT TCTCCCCCTG 480

CCAGTCTCTT CTGATTAAAG AGATCTGTTC TGGGTGTTGA CCACTCCAGA GAAGTTTCGA 540

GGGGTCCTCA CCTGGTTGAC CCAAAAATGT TCCCTTGACC ATTGGCTGCG CTAACCCCCA 600

GCCCACAGAG CCTGAATTTG TAAGCAACTT GCTTCTAAAT GCCCAGTTCA CTTCTTTGCA 660

GAGC 664

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(vi) ORIGINAL SOURCE:
(A) ORGANISM: SYNTHETIC OLIGONUCLEOTIDE

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..27
(D) OTHER INFORMATION: /note= "ANTISENSE TO POSITIONS 927-953 OF SEQ ID NO.: 1."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CTGCTGCTGT TGCTGAAGGA GTTGCAT 27

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(vi) ORIGINAL SOURCE:
(A) ORGANISM: SYNTHETIC OLIGONUCLEOTIDE

(ix) FEATURE:
(A) NAME/KEY: misc_feature

(B) LOCATION: 1..21
(D) OTHER INFORMATION: /note= "ANTISENSE TO POSITIONS 916-936 OF SEQ ID NO.: 1."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GGAGTTGCAT GGTGCTGGCC TCAGCACCA 29

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(vi) ORIGINAL SOURCE:
(A) ORGANISM: SYNTHETIC OLIGONUCLEOTIDE

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..21
(D) OTHER INFORMATION: /note= "ANTISENSE TO POSITIONS 927-947 OF SEQ ID NO.: 1."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CTGTTGCTGA AGGAGTTGCA TAACTCCTT 29

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(vi) ORIGINAL SOURCE:
(A) ORGANISM: SYNTHETIC OLIGONUCLEOTIDE

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..25
(D) OTHER INFORMATION: /note= "ANTISENSE TO POSITIONS 611-635 OF SEQ ID NO.: 2."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GGGCTGTGAA GGTGGTGATT TCCCC 25

CLAIMS

We claim:

1. A method for treating a patient diagnosed as having benign prostatic hyperplasia or a prostatic cancer comprising

administering to said patient a therapeutically effective amount of a composition comprising an antisense oligonucleotide which selectively hybridizes to a gene or mRNA sequence of said patient;

wherein said antisense inhibits expression of said gene or mRNA sequence; and

wherein said gene or mRNA sequence is selected from the group consisting of an AR and an αFGF gene or mRNA sequence.

2. A method as in claim 1 wherein said oligonucleotide is selected from the group consisting of

(a) oligonucleotides comprising at least 10 consecutive bases from SEQ ID NO.: 1;

(b) oligonucleotides comprising at least 10 consecutive bases from a genomic sequence corresponding to SEQ ID NO.: 1; and

(c) oligonucleotides that hybridize to the complements of the oligonucleotides of (a) or (b) under physiological conditions.

3. A method as in claim 1 wherein said oligonucleotide is selected from the group consisting of

(a) oligonucleotides comprising at least 20 consecutive bases from SEQ ID NO.: 1;

(b) oligonucleotides comprising at least 10 consecutive bases from a genomic sequence corresponding to SEQ ID NO.: 1; and

(c) oligonucleotides that hybridize to the complements of the oligonucleotides of (a) or (b) under physiological conditions.

4. A method as in claim 1 wherein said oligonucleotide is selected from the group consisting of

(a) oligonucleotides comprising at least 10 consecutive bases from the group consisting of SEQ ID NO.: 2, SEQ ID NO.: 3 and SEQ ID NO.: 4;

(b) oligonucleotides comprising at least 10 consecutive bases from the joined exons of SEQ ID NO. : 2, SEQ ID NO.: 3 and SEQ ID NO.: 4; and

(c) oligonucleotides that hybridize to the complements of the oligonucleotides of (a) or (b) under physiological conditions.

5. A method as in claim 1 wherein said oligonucleotide is selected from the group consisting of

(a) oligonucleotides comprising at least 20 consecutive bases from the group consisting of SEQ ID NO.: 2, SEQ ID NO.: 3 and SEQ ID NO.: 4;

(b) oligonucleotides comprising at least 20 consecutive bases from the joined exons of SEQ ID NO. : 2, SEQ ID NO.: 3 and SEQ ID NO.: 4; and

(c) oligonucleotides that hybridize to the complements of the oligonucleotides of (a) or (b) under physiological conditions.

6. A method as in claim 1 wherein said oligonucleotide comprises a nucleotide sequence selected from the group consisting of SEQ ID NO.: 5, SEQ ID NO.: 6, SEQ ID NO.: 7, and SEQ ID NO.: 8.

7. A method as in claim 1 wherein said oligonucleotide is a modified oligonucleotide.

8. A method as in claim 7 wherein said oligonucleotide is a modified oligonucleotide including at least one synthetic internucleoside linkage.

9. A method as in claim 8 wherein said synthetic internucleoside linkage is selected from the group consisting of phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate

triesters, acetamidates, and carboxymethyl esters.

10. A method as in claim 7 wherein said oligonucleotide is a modified oligonucleotide having at least one low molecular weight organic group covalently bound to a phosphate group of said oligonucleotide.

11. A method as in claim 7 wherein said oligonucleotide is a modified oligonucleotide having at least one low molecular weight organic group covalently bound to a 2' position of a ribose of said oligonucleotide.

12. A method as in claim 7 wherein said oligonucleotide is a modified oligonucleotide having covalently attached thereto a compound selected from the group consisting of androgen, androgen derivatives, estrogen, estrogen derivatives, estramustine, emcyt and estracyt.

13. A method as in claim 1 wherein said oligonucleotide is administered intravenously at a dosage between 1.0 μg and 100 mg per kg body weight of said patient.

14. A method as in claim 1 wherein said patient has a prostatic cancer which is refractory to anti-androgen or estrogen hormonal therapy.

15. A pharmaceutical composition comprising

a sterile pharmaceutically acceptable carrier; and

a therapeutically effective amount of an isolated antisense oligonucleotide which selectively hybridizes to a gene or mRNA sequence of a patient;

wherein said antisense inhibits expression of said gene or mRNA sequence; and

wherein said gene or mRNA sequence is selected from the group consisting of an AR and an αFGF gene or mRNA sequence.

16. A composition as in claim 15 wherein said oligonucleotide is selected from the group consisting of

(a) oligonucleotides comprising at least 10 consecutive bases from SEQ ID NO.: 1;

(b) oligonucleotides comprising at least 10 consecutive bases from the joined exons of SEQ ID NO.: 1; and

(c) oligonucleotides that hybridize to the complements of the oligonucleotides of (a) or (b) under physiological conditions.

17. A composition as in claim 15 wherein said oligonucleotide is selected from the group consisting of

(a) oligonucleotides comprising at least 20 consecutive bases from SEQ ID NO.: 1;

(b) oligonucleotides comprising at least 20 consecutive bases from the joined exons of SEQ ID NO.: 1; and

(c) oligonucleotides that hybridize to the complements of the oligonucleotides of (a) or (b) under physiological conditions.

18. A composition as in claim 15 wherein said oligonucleotide is selected from the group consisting of

(a) oligonucleotides comprising at least 10 consecutive bases from SEQ ID NO.: 2;

(b) oligonucleotides comprising at least 10 consecutive bases from a genomic sequence corresponding to SEQ ID NO.: 2; and

(c) oligonucleotides that hybridize to the complements of the oligonucleotides of (a) or (b) under physiological conditions.

19. A composition as in claim 15 wherein said oligonucleotide is selected from the group consisting of

(a) oligonucleotides comprising at least 20 consecutive bases from SEQ ID NO.: 2;

(b) oligonucleotides comprising at least 20 consecutive bases from a genomic sequence corresponding to SEQ ID NO.: 2; and

(c) oligonucleotides that hybridize to the complements of the oligonucleotides of (a) or (b) under physiological conditions.

20. A composition as in claim 15 wherein said oligonucleotide comprises a nucleotide

sequence selected from the group consisting of SEQ ID NO.: 5, SEQ ID NO.: 6, SEQ ID NO.: 7, SEQ ID NO.: 8, and SEQ ID NO.: 9.

21. A composition as in claim 15 wherein said oligonucleotide is a modified oligonucleotide.

22. A composition as in claim 15 wherein said oligonucleotide is a modified oligonucleotide including at least one synthetic internucleoside linkage.

23. A composition as in claim 22 wherein said synthetic internucleoside linkage is selected from the group consisting of phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamidates, and carboxymethyl esters.

24. A composition as in claim 21 wherein said oligonucleotide is a modified oligonucleotide having at least one low molecular weight organic group covalently bound to a phosphate group of said oligonucleotide.

25. A composition as in claim 21 wherein said oligonucleotide is a modified oligonucleotide having at least one low molecular weight organic group covalently bound to a 2' position of a ribose of said oligonucleotide.

26. A composition as in claim 21 wherein said oligonucleotide is a modified oligonucleotide having covalently attached thereto a compound selected from the group consisting of androgen, androgen derivatives, estrogen, estrogen derivatives, estramustine, emcyt and estracyt.

27. A pharmaceutical kit comprising the pharmaceutical composition of claim 15 in a pharmaceutically acceptable carrier for intravenous administration.

28. A method for treating a patient diagnosed as having benign prostatic hyperplasia

or a prostatic cancer comprising

administering to said patient a therapeutically effective amount of a composition comprising an antisense oligonucleotide which selectively hybridizes to a gene or mRNA sequence of said patient;

wherein said antisense inhibits expression of said gene or mRNA sequence; and

wherein said antisense inhibits or represses prostatic cell growth.

29. A method as in claim 28 wherein said gene is selected from the group consisting of a PSA gene, a probasin gene, an αFGF gene, an androgen receptor gene, an estrogen receptor gene, a telomerase gene, a prohibitin gene, a src gene, a ras gene, a myc gene, a blc-2 gene, a protein kinase-A gene, a plasminogen activator urokinase gene and a methyl transferase gene.

INTERNATIONAL SEARCH REPORT

Internation: pplication No
PCT/US 96/15081

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 C07H21/04 A61K31/70 //A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07H A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 05268 A (BAYLOR COLLEGE MEDICINE) 17 March 1994 see page 8, line 14 - page 10, line 20 see example 1 see claims 1,2,17-21,32-35 ---	1,7,13, 15,21, 28,29
X	WO 89 09791 A (UNIV NORTH CAROLINA) 19 October 1989 see page 2, line 12 - line 32 see page 24 ---	1,28,29
X	WO 95 11301 A (UNIV MICHIGAN) 27 April 1995 see claims --- -/--	28,29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
14 February 1997	26.02.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Andres, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CANCER RESEARCH, (1994 MAY 1) 54 (9) 2372-7., XP002025258 ACHBAROU, A. ET AL.: "Urokinase overproduction results in increased skeletal metastasis by prostate cancer cells in vivo." see the whole document	28,29
A	CANCER SURVEYS, vol. 11, 1991, pages 239-254, XP000616360 SHERIDAN, V. & TEW, K.: "Mechanism based chemotherapy for prostate cancer" cited in the application see the whole document	12,26
O,A	ANTISENSE RES.DEV. 5 (FALL 1995); PAGE 239; ABSTRACT III12, XP002025259 HEAD, M. ET AL.: "Penetration and stability of antisense oligonucleotides injected into the early embryonic chick eye" see abstract & INT.CONF.:'THERAPEUTIC OLIGONUCLEOTIDES FROM CELL TO MAN'; 4 TO 7 APRIL 1995; SEILLAC; FRANCE,	1,4-9
P,X	US 5 556 956 A (ROY ARUN K ET AL) 17 September 1996 see the whole document	1,7-10, 13,15, 21-24, 27-29
P,X	CELL GROWTH AND DIFFERENTIATION, (1996 MAY) 7 (5) 573-86., XP000616505 SHAIN, S. ET AL.: "Endogenous fibroblast growth factor - 1 or fibroblast growth factor -2 modulate prostate cancer cell proliferation." see the whole document	1,4-9, 28,29
P,X	JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 MAY 31) 271 (22) 13228-33., XP002025260 BOFFA, L. ET AL.: "Invasion of the CAG triplet repeats by a complementary peptide nucleic acid inhibits transcription of the androgen receptor and TATA-binding protein genes and correlates with refolding of an active nucleosome containing a unique AR gene sequence." see the whole document	1-3,7,8, 10,28,29
P,X	WO 96 03875 A (UNIV EMORY) 15 February 1996 see page 11, line 12 - page 13, line 21	28,29 12,26

-/--

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
O,P, X	PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING 37 (0), March 1996, page 344 XP002025261 STEINER, M. ET AL.: "Gene therapy of advanced prostate cancer by in vivo transduction with prostate-targeted antisense c- myc RNA retroviruses." see abstract #2349 & 87TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, WASHINGTON, D.C., USA, APRIL 20-24, 1996., -----	28,29

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INTERNATIONAL SEARCH REPORT

Intern: al application No.
PCT/US 96/ 15081

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see Further Information sheet enclosed.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant s protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 15081

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Remark : Although claims 1-14, 28-29 (as far as in vivo methods are concerned) are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US 96/15081

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9405268	17-03-94	AU-A- 4846793	29-03-94
WO-A-8909791	19-10-89	EP-A- 0365657	02-05-90
WO-A-9511301	27-04-95	AU-A- 7983294	08-05-95
US-A-5556956	17-09-96	NONE	
WO-A-9603875	15-02-96	AU-A- 3071995	04-03-96

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